REMARKS

I. Background

The present Amendment is in response to the Office Action mailed December 31, 2007. Since claims 1-43 have been previously cancelled, claims 44-72 were pending in the application for consideration at the time of the mailing of the Office Action. Claims 44-46 are currently amended. Claims 55-72 are currently cancelled. New claims 73-82 are currently added. Thus, claims 44-54 and 73-82 are currently pending for consideration.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicant's remarks are presented in the order in which the corresponding issues were raised in the Office Action.

Please note that the following remarks are not intended to be an exhaustive enumeration of the distinctions between any cited references and the claimed invention. Rather, the distinctions identified and discussed below are presented solely by way of example to illustrate some of the differences between the claimed invention and the cited references. In addition, Applicant requests that the Examiner carefully review any references discussed below to ensure that Applicant's understanding and discussion of the references, if any, is consistent with the Examiner's understanding.

II. Proposed Claim Amendments

Please amend the claims in the manner indicated above, where an underline represents new text, and strikeouts are used to indicate deleted text. The amendments to claims 44-46 are fully supported by direct and inherent teachings included in the specification of the published application (PG-PUB 2003/0082564) in at least paragraphs [0001], [0012], [0026], [0027], [0036], [0059], [0060], [0063], [0081], [0118], [0128-0133], and the Examples.

New claim 73 is fully supported by the application as originally filed in at least paragraph [0034] (PG-PUB 2003/0082564).

New claim 74 is fully supported by the application as originally filed in at least paragraph [0016] (PG-PUB 2003/0082564).

New claim 75 is fully supported by the application as originally filed in at least paragraph [0131] (PG-PUB 2003/0082564).

New claim 76 is fully supported by the application as originally filed in at least paragraphs [0016] and [0125] (PG-PUB 2003/0082564).

New claim 77 is fully supported by the application as originally filed in at least paragraph [0190] (PG-PUB 2003/0082564).

New claims 78-79 are fully supported by the application as originally filed in at least paragraphs [0042-0054] (PG-PUB 2003/0082564).

New claims 80-82 are fully supported by the application as originally filed in at least paragraphs [0031-0033], [0038-0039], and [0110] (PG-PUB 2003/0082564).

In view of the foregoing, Applicant respectfully submits that the amendments and new claims do not introduce new matter and entry thereof is respectfully requested.

III. Rejection on the Merits

A. Rejections Under 35 U.S.C. § 112, First Paragraph

The Office Action rejects claim 48 under 37 CFR § 112, first paragraph, as failing to comply with the written description requirement. Applicant respectfully asserts that a "synthetic chemical compound" is fully supported by the specification at paragraph [0118] (PG-PUB 2003/0082564). This paragraph states the compounds can be "prepared by organic synthesis," which fully supports "synthetic chemical compound" as recited in claim 48. Thus, Applicant respectfully requests withdrawal of this rejection.

B. Rejections Under 35 U.S.C. § 102

The Office Action rejects claims 44-52 under 35 U.S.C. § 102(b) as being anticipated by *Htun et al* (PNAS, 1996) as evidenced by *Carey et al.* (J. Cell Biol., June 1996) or *Agarwal* (Pharmacol. Ther., 1996). Applicant respectfully traverses this rejection because *Htun*, even when viewed with evidence of *Carey* or *Agarwal*, does not teach or suggest each and every element of the presently claimed invention.

In accordance with Applicant's understanding *Htun* teaches a fusion protein (GR-GFP) of a glucocorticoid receptor (GR) and green fluorescent protein (GFP) encoded by a nucleic acid that is transiently transfected into cells (page 4845, second column). The cells that expressed the GR-GFP (e.g., only 10% of cells were transfected) were then subjected to known compounds having known activities with GR to determine whether the GR-GFP was a suitable fusion protein

for studying GR (page 4847, second column). *Htun* teaches that dexamethasone, RU486, progesterone, and 17beta-estradiol each had a known activity with GR and each compound maintained the activity with the fusion protein GR-GFP (page 4847, second column). The cells were only evaluated as living cells in a perfusion chamber, and thereby the cells were not fixed or evaluated in a screening format (e.g., microtiter or multi-well plate). The living cells were examined manually with time-lapse video, confocal microscopy, and a manual microscope where images were acquired manually every 15 seconds with a charge-coupled device camera on a workstation using custom software and incorporating functions from a vendor-supplied library (page 4846, first column). Nothing in *Htun* teaches or suggests that the images taken by the video, confocal microscope, or manual microscope with camera were analyzed with custom software, but does teach visual, qualitative analysis (page 4847, first and second columns). *Htun* is completely devoid of introducing a compound with an unknown activity with GR into the cells that expressed GR-GFP to determine whether or not the compound is biologically active with GR. Since only known compounds with known activities as ligands for GR were tested with GR-GFP, *Htun* does not teach or suggest screening compounds with GR-GFP to determine whether the compounds have a biological function or biological effect on GR. In fact, *Htun* never describes screening, and only studied known compounds with known activities as ligands for GR because "it [was] essential to examine whether any GR activity has been compromised by GFP" (page 4849, first column). Thus, *Htun* does not teach or suggest screening a library of compounds to detect a biologically active compound, and does not teach or suggest that GR-GFP can be used to determine whether or not a compound has a biological function or biological effect on GR.

Additionally, Applicant respectfully asserts that the skilled artisan would not be motivated by the teachings of *Htun* to use the experiments and GR-GFP described therein for screening compounds for biological function or biological effect. In part, this is because the experimental techniques employed in *Htun* are manual, and thereby extremely rigorous and time consuming such that any experiment employed with such techniques would be inadequate for screening a library of compounds. Additionally, 10% transient transfection is not adequate for screening applications. The fact that a skilled artisan would not employ the techniques of *Htun* in screening a library of compounds is evidenced by only 4 known ligands to the GR receptor being used to determine whether the GFP compromised the activity of the GR in the GR-GFP fusion protein. Thus, a skilled artisan would not consider *Htun* to have teachings or suggestion

for screening a library of compounds because the experimental protocols of *Htun* are not suitable for screening a library of compounds.

In accordance with Applicant's understanding, the teachings of *Carey* are similar to *Htun* and has the same problems and deficiencies. The evidence provided in *Carey* only reinforces the deficiencies of *Htun* because of at least the following: *Carey* does not teach or suggest a screening experiment; *Carey* does not teach or suggest screening a library of compounds to detect a biologically active compound; *Carey* only teaches or suggests manual image acquisition, which is unsuitable for screening applications; and *Carey* only teaches transiently transfected cells with only a 30% efficiency. Thus, the evidence of *Carey* supports that *Htun* does not teach screening a library of compounds or any suitable screening protocols, and thereby, a skilled artisan would not consult or use the experimental protocols of *Htun* or *Carey* for screening a library of compounds.

In accordance with Applicant's understanding, the teachings of *Agarwal* are only relevant with respect to a GR being capable of forming a complex with a ligand. *Agarwal* is completely silent as to GR-GFP and does not teach or suggest screening a library of compounds to detect a biologically active compound. Thus, *Agarwal* does not provide evidence that a skilled artisan would consult or use the experimental protocols of *Htun* or *Carey* for screening a library of compounds.

Applicant respectfully asserts that *Htun*, even when viewed with evidence of *Carey* or *Agarwal*, does not teach or suggest a "method for screening a library of compounds to detect a biologically active compound by detecting intracellular translocation of a subunit of a component," as recited in claims 44-46. Applicant respectfully asserts that the Declaration of Chris Ireland (Declaration), which was submitted in the prosecution of the instant patent application on March 20, 2007, should be considered respect to the definition of "library of compounds" and "screening a library of compounds." In view of the Declaration, the combination of dexamethasone, RU486, progesterone, and 17beta-estradiol do not constitute a "library of compounds." While Applicant and the Declaration have not recited a specific number of compounds to constitute a "library of compounds," a skilled artisan would not consider 4 compounds to be a "library of compounds." This is similar to 4 books not being considered to be a library of books. Also, *Htun* does not teach a "process to systematically examine, test, or evaluate the compounds of the library of compounds in order to determine suitability for a particular purpose, or to detect wanted or unwanted attributes of the compounds" (Declaration of

Chris Ireland, paragraph 13) with respect to a library of compounds. The 4 compounds recited in *Htun* were already known to have activity with GR, and therefore are not being screened to detect biological activity in the context of claims 44-46.

The American Heritage® Dictionary of the English Language defines "detect" to mean "to discover or ascertain the existence, presence, or fact of."[1] Applicant respectfully asserts that the known existence, presence, or fact that dexamethasone, RU486, progesterone, and 17beta-estradiol each had a known activity with GR prior to the publication of *Htun* establishes that *Htun* does not teach or suggest a method for "detecting a biologically active compound by detecting intracellular translocation of a subunit of a component." Since the biological activity of the 4 compounds was known, such activity could not be discovered or detected in the context of claims 44-46.

Additionally, Applicant respectfully asserts that *Htun* does not teach or suggest "screening the library of compounds to determine whether the at least one compound of the library of compounds has a biological function or biological effect on the subunit in the one or more cells," as recited in claims 44-46. *Htun* does not teach or suggest any experimental protocol for "screening" to be performed with the intent to determine whether any of the 4 compounds has a biological function or biological effect on GR because the experimental protocols are inadequate for screening a library of compounds and it was already known that the 4 compounds had a known activity for GR.

Applicant also respectfully asserts that *Htun*, even when viewed with evidence of *Carey* or *Agarwal*, does not teach or suggest that "translocation of the subunit in response to the at least one compound of the library of compounds determines that the at least one compound has a biological function or biological effect on the subunit," as recited in claims 44-46. In part, this is because *Htun* does not teach that translocation of a subunit of a component in response to a compound can be used to determine that the compound has a biological function or biological effect on the subunit. In fact, *Htun* does not teach inducing translocation with a compound in order to determine whether or not the compound is biologically active.

The *Carey* and/or *Agarwal* references do not cure the deficiencies of *Htun* described above. That is, neither *Carey* nor *Agarwal* teach or suggest the claim elements recited above that *Htun* does not teach. In fact, *Carey* and/or *Agarwal* are only provided as evidence that GR forms

[1] *The American Heritage® Dictionary of the English Language, Fourth Edition Published by Houghton Mifflin Company. All rights reserved.*, © 2006 by Houghton Mifflin Company.

complexes with other substances within cells to form a component comprised of the GR and other substance in order to characterize GR as a subunit of a component.

In view of the foregoing, Applicant respectfully asserts that *Htun*, even when viewed with evidence of *Carey* or *Agarwal*, does not teach or suggest each and every element of the presently pending claims. Thus, *Htun*, even when viewed with evidence of *Carey* or *Agarwal*, does not anticipate the presently claimed invention of claims 44-46.

Since Claims 47-54 depend from claims 44, 45, and/or 46, such claims include the limitations thereof and are allowable for the same reasons claims 44-46 are allowable. Accordingly, Applicant respectfully requests withdrawal of the rejection to claims 44-52 under 35 U.S.C. § 102(b).

C. Rejections Under 35 U.S.C. § 103

The Office Action rejects claims 53-54 under 35 U.S.C. § 103(a) as being unpatentable over *Htun et al* (PNAS, 1996) as evidenced by *Carey et al.* (J. Cell Biol., June 1996) in view of *Agarwal* (Pharmacol. Ther., 1996) and *Sonenberg et al* (U.S. Patent 5,874,231). Applicant respectfully traverses this rejection because *Htun*, even when viewed with evidence of *Carey*, in view of *Agarwal* and *Sonenberg* does not establish a *prima facie* case of obviousness with respect to the presently claimed invention.

The foregoing discussions of *Htun*, *Carey*, and *Agarwal* references are applicable to this rejection and incorporated into this remark by specific reference. Additionally, in accordance with Applicant's understanding, *Agarwal* teaches that steroids can stimulate transcription and thereby increase translation from mRNA to protein synthesis (page 186, first column), and are thereby transcription factors. Figure 1 shows the model of transcription activation. *Agarwal* goes on to teach the structures of some antiglucocorticoids (e.g., figure 2). Additionally, *Agarwal* indicates that some antiglucocorticoids can be used in the treatments of some diseases, probably through gene expression regulation. For example, RU38486 antagonizes the transcription suppression by glucocorticoids (page 200, first column). However, *Agarwal* is completely devoid of teaching or suggesting a GR-GFP fusion protein. *Agarwal* is also devoid of teaching or suggesting screening experiments to detect biologically active compounds. Additionally, *Agarwal* is devoid of teaching or suggesting that translocation of a fusion protein that includes GR can be used to determine that a compound has a biological function or biological effect on GR. Thus, a skilled artisan would not consider *Agarwal* in designing an

experimental protocol suitable for screening a library of compounds.

In accordance with Applicant's understanding, *Sonenberg* teaches methods of screening a library of compounds that modulate the translation of mRNA to protein by a cellular component and a translation factor (Abstract). In fact, *Sonenberg* is only concerned with modulating translation from mRNA to protein, and is not concerned with translocation within a cell. It should be noted that translation and translocation are completely different cellular processes and are not interchangeable with respect to cell function or assays of the same. *Sonenberg* teaches that certain cellular components interact with translation factors to translate mRNA to a protein, and the invention is screening "a large number of potentially useful agents," which is "a process distinct from a single experiment in which a single agent is studied in detail" (column 2, lines 25-30) to determine if the potentially useful agent modulates translation from mRNA to protein. *Sonenberg* teaches "modulation of translation" to be a control or change of control of the efficiency or rate of translation of mRNAs which results in a change in the overall rate of protein synthesis (column 3, lines 18-24). Since studying translation is much different from studying translocation, *Sonenberg* is completely devoid of teaching or suggesting a GR-GFP fusion protein or any means of studying translocation. *Sonenberg* is also devoid of teaching or suggesting screening experiments to detect biologically active compounds by detecting intracellular translocation. Additionally, *Sonenberg* is devoid of teaching or suggesting that translocation of GR can be used to determine that a compound has a biological function or biological effect on the GR. Thus, a skilled artisan would not consider *Sonenberg* in designing an experimental protocol suitable for screening a library of compounds by determining a variation in translocation in response to a compound in order to determine that the compound has a biological function or biological effect.

Since *Htun* teaches a GR-GFP to monitor translocation; and neither *Agarwal* nor *Sonenberg* teach or suggest a GR-GFP or monitoring translocation, the combination of references could only be made with use of impermissible hindsight after first reviewing the instant patent application. Only Applicant's patent application teaches the use of a fusion protein for screening a library of compounds to detect biologically active compounds by detecting a variation of translocation of the fusion protein within a cell. Thus, Applicant's patent application must have been consulted and used as a roadmap for making the proposed combination of references.

Applicant respectfully asserts that there is no valid reason for making the proposed

combination of *Htun*, *Agarwal*, and *Sonenberg*, and such a combination is improper. *Htun* is mainly directed to teaching that a GR-GFP can be used to study translocation of GR because the GFP does not compromise the activity of the GR. *Htun* does not teach or suggest anything with regard to GR antagonists that modulate transcription being studied for treatment of diseases, or teach or suggest anything with regard to compounds being screened for activity in modulating translation from mRNA to DNA. *Agarwal* is mainly directed to teaching that GR antagonists that modulate transcription can be used to treat diseases. *Agarwal* does not teach or suggest a GR-GFP or other fusion protein for use in any experiment, or teach or suggest any experiment to monitor translocation of GR within a cell. *Agarwal* also does not teach or suggest screening the GR antagonists to determine if they modulate interactions between cellular components and translation factors to modulate translation of mRNA to proteins. *Sonenberg* is mainly directed to screening compounds for activity in modulating interactions between cellular components and translation factors to modulate translation of mRNA to proteins. *Sonenberg* does not teach or suggest a GR-GFP for use in any screening experiment, or teach or suggest any screening experiment to monitor translocation within a cell. *Sonenberg* also does not teach or suggest screening GR antagonists that modulate transcription. Thus, there is no valid reason for making the proposed combination of *Htun*, *Agarwal*, and *Sonenberg* because each of the references are unique in their teachings and nothing within the individual references provides a valid reason for being combined with the other references.

Applicant respectfully asserts that *Htun*, *Agarwal*, and *Sonenberg*, alone or in combination, do not teach or suggest each and every element of the presently pending claims. More particularly, the combination of references does not teach or suggest a "method for screening a library of compounds to detect a biologically active compound by detecting intracellular translocation of a subunit of a component," as recited in claims 44-46. As recited above, *Htun* does not teach a method of screening a library of compounds in the context of claims 44-46. Additionally, none of the recited references, alone or in combination teaches or suggests that that a biologically active compound can be detected by detecting intracellular translocation of a subunit of a component.

Applicant also respectfully asserts that the combination of references does not teach or suggest that "translocation of the subunit in response to the at least one compound of the library of compounds determines that the at least one compound has a biological function or biological effect on the subunit," as recited in claims 44-46. In part, this is because none of *Htun*, *Agarwal*,

and/or *Sonenberg* teach or suggest that translocation of a subunit of a component in response to a compound can be used to determine that the compound has a biological function or biological effect on the subunit. In fact, none of the references teach or suggest attempting to induce translocation with a compound in order to determine whether or not the compound is biologically active.

In view of the foregoing, Applicant respectfully asserts that the combination of references could only be made with impermissible hindsight and using the Applicant's patent application as a roadmap, that the references themselves to not provide any valid reason to be combined with each other, and that the combination of references does not teach or suggest each and every element of claims 44-46. Accordingly, the Office Action has not established a *prima facie* case of obviousness, and claims 44-46 are allowable. Since claims 47-52 depend from claims 44, 45, or 46, such claims include the limitations thereof and are allowable for the same reasons claims 44-46 are allowable. Accordingly, Applicant respectfully requests withdrawal of the rejection to claims 44-52 under 35 U.S.C. § 103(a).

The Office Action rejects claims 53-54 under 35 U.S.C. § 103(a) as being unpatentable over *Htun*, *Carey*, *Agarwal*, and *Sonenberg* as applied to claims 44-52 above, and further in view of *Cormack at al.* (Gene, 1996). Applicant respectfully traverses the rejection because a *prima facie* case of obviousness has not been established.

The foregoing discussions of *Htun*, *Carey*, *Agarwal*, and *Sonenberg* references are applicable to the instant rejection and incorporated into this remark by specific reference.

The Office Action cites *Cormack* because it teaches "mutations of GFP, including the F64L and S65T." (Final Office Action, page 6.) However, *Cormack* does not cure the deficiencies recited above with respect to *Htun*, *Carey*, *Agarwal*, and *Sonenberg*.

Claims 53-54 depend from claims 44-46, and thus incorporate the limitations thereof. As such, Applicant respectfully asserts the combination of *Htun*, *Carey*, *Agarwal*, *Sonenberg,* and *Cormack* does not teach or suggest each and every element of the claimed invention. Specifically, the combination of *Htun*, *Carey*, *Agarwal*, *Sonenberg,* and *Cormack* does not teach or suggest the elements of claims 44-46 as recited above that are not taught or suggested by *Htun*, *Carey*, *Agarwal*, and *Sonenberg*, alone or in combination, and thereby the combination of *Htun*, *Carey*, *Agarwal*, *Sonenberg,* and *Cormack*, and *Cormack* does not teach or suggest the elements recited in claims 53-54.

Since the combination of *Htun*, *Carey*, *Agarwal*, *Sonenberg*, and *Cormack* does not teach or suggest each and every element of claims 53-54, a *prima facie* case of obviousness has not been established. Accordingly, Applicant respectfully requests withdrawal of the rejection to claims 53-54 under 35 U.S.C. § 103(a).

IV. New Claims

Applicant respectfully submits that new claims 73-82 are not anticipated or obvious in view of the art cited in the Office Action, and are allowable for at least the same reasons claims 44-52 are allowable. In part, claims 73-82 depend from claims 44-46 and thereby include the limitations thereof. In view of the foregoing, applicant submits that claims 73-82 are allowable over the cited prior art.

SUMMARY

In view of the foregoing, Applicant respectfully submits that the other rejections to the claims are now moot and do not, therefore, need to be addressed individually at this time. It will be appreciated, however, that this should not be construed as Applicant acquiescing to any of the purported teachings or assertions made regarding the cited art or the pending application, including any Official Notice. Instead, Applicant reserves the right to challenge any of the purported teachings or assertions made in any action at any appropriate time in the future, should the need arise. Furthermore, to the extent that the Examiner has relied on any Official Notice, explicitly or implicitly, Applicant specifically requests that the Examiner provide references supporting the teachings officially noticed, as well as the required motivation or suggestion to combine the relied upon Notice with the other art of record.

Applicant believes the amendments to the claims have placed claims 44-54 in allowable form. Additionally, Applicant believes new claims 73-82 are allowable. Thus, Applicant respectfully requests reconsideration of the application and allowance of the presently pending claims.

In the event that the Examiner finds remaining impediment to a prompt allowance of this application that may be clarified through a telephone interview, the Examiner is requested to contact the undersigned attorney.

Dated this 27th day of March, 2008.

Respectfully submitted,

/Jonathan M. Benns, Reg. #53983/

JONATHAN M. BENNS
Registration No. 53,983

DANA L. TANGREN
Registration No. 37,246
Attorneys for Applicant(s)
WORKMAN NYDEGGER
(801) 533-9800

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